(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/058793 A1

(51) International Patent Classification[7]: A61P 9/00, A61K 45/06, 3/23

(21) International Application Number: PCT/EP02/00507

(22) International Filing Date: 16 January 2002 (16.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2001A000129 25 January 2001 (25.01.2001) IT

(71) Applicant *(for all designated States except US)*: **PHARMACIA ITALIA S.P.A.** [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GRANATA, Francesco** [IT/IT]; Via Madonnina, 19, I-20121 Milano (IT). **PAMPARANA, Franco** [IT/IT]; Piazza Firenze, 19, I-20149 Milano (IT). **STRAGLIOTTO, Eduardo, Lino** [IT/IT]; Corso XXII Marzo, 43, I-20129 Milano (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/058793 A1

(54) Title: ESSENTIAL N-3 FATTY ACIDS IN CARDIAC INSUFFICIENCY AND HEART FAILURE THERAPY

(57) Abstract: The present invention concerns a method of therapeutic prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure including the administration of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), either alone or in combination with another therapeutic agent.

ESSENTIAL N-3 FATTY ACIDS IN CARDIAC INSUFFICIENCY AND HEART FAILURE THERAPY

The present invention belongs to the field of pharmaceutical chemistry and cardiovascular medicine and provides a method of prevention and management of cardiac insufficiency and heart failure: two heart diseases in which the second one is the result of the progressive evolution of the first one.

Cardiac insufficiency is a condition in which the heart pump function is inadequate to meet the bodily metabolic requirements. Depending on the different severity of the pump deficit, cardiac insufficiency may be symptom-free or clinically manifest.

Cardiac insufficiency could have various causes, e.g.:

- disorders of myocardial function, which is the most frequent cause, due to a reduced contractility, but also to a loss of contractile tissue;
- a volume load, due to disorders requiring the ventricle to expel more blood than the normal per minute;
- a pressure load, due to disorders increasing the resistance to the outflow from the ventricles.

Heart failure is the result of the progressive evolution of cardiac insufficiency.

Moreover, a broad spectrum of diseases could cause an impaired filling or emptying of heart chambers, such as: the diseases resulting from a monogenic (familial hypertrophic cardiomyopathy, mitochondral cardiomyopathies) or multigenic defect which are bound to environmental factors such as cigarette smoking, diet, physical exercise, secondary heart diseases. All these diseases take the "common end path" towards heart failure, which sees at first an impairment of the molecular mechanisms and then an impairment of the ventricular function and heart failure. Therefore, heart failure is a syndrome with a various etiology resulting from an anatomo-functional anomaly of the heart with inability in keeping a stroke adequate to the metabolic requirements of the tissues or maintaining the stroke volume by a high filling pressure.

Heart failure is characterized by clinical signs and symptoms secondary to the inadequate response to the body metabolic requirements. This condition could occur acutely or have a chronic course.

The pathophysiological interpretations of heart failure have had a remarkable evolution in time. This syndrome was considered as a pump deficiency associated with a renal dysfunction in years '50-'60, a pump dysfunction associated with an increase in peripheral resistance in years '70-'80 and is considered at present as a failure of the pump function associated with the neuro-hormonal activation with resulting hemodynamic impairments which take to a dysfunction of many organs and apparatuses.

The present drug therapy of cardiac "pump function" includes the use of drugs acting by various modes of action on different points of the etiopathogenesis of the diseases. We mention as an example: ACE-inhibitors (Angiotensin Converting Enzymes inhibitors), diuretics, non-digitalis positive inotropic drugs such as adrenergics and inhibitors of phosphodiesterase, arteriolar and venular vasodilators, e.g. hydralazine and isosorbide dinitrate, beta-blockers e.g. metoprolol and bisoprolol and digitalis derivatives, e.g. digotoxin.

Heart failure is at present one of the most important causes of morbidity and mortality in the industrialized countries, as clearly demonstrated by the present case-series: in USA 4.7 million persons have a congestive heart failure, with an incidence equal to 400,000 new cases a year.

The prevalence of chronic cardiac insufficiency rises from 8 cases of heart failure out of 1,000 subjects of age ranging from 50 to 59 years, to 66 cases out of 1,000 subjects between 80 and 89 years.

If we consider that about 35% of patients with heart failure are hospitalised at least once a year and that 80% of men and 65% of women die within 6 years, the social-health entity of the problem emerges in its full dramatic evidence.

Moreover, the incidence of heart failure seems to increase paradoxically with the reduction of death rate for myocardial infarction and for other cardiovascular diseases. The ageing of the population seems to be a contributing factor to amplify the relevance of the phenomenon.

Therefore, there is the need of a safe and convenient method of prevention and therapeutic treatment of cardiac insufficiency and heart failure, in particular in elderly patients, in order to restore (or to control) the usual pump function of the heart.

The present invention provides a method for the prevention and therapeutic treatment of cardiac insufficiency and heart failure in a patient in need of this treatment comprising the administration to such patient of a therapeutically effective amount of an essential fatty acid containing a mixture of (20:5ω 3) eicosapentaenoic acid ethyl ester (EPA) and of (20:6ω 3) docosahexaenoic acid ethyl ester (DHA), either alone or in combination with another therapeutic agent.

It is well known in the art that some essential fatty acids, in particular ω 3 PUFA, contained for example in the fish oil, have a therapeutic effect in the prevention and therapy of cardiovascular disorders, e.g. in the prevention and treatment of atherothrombotic events and hyperlipidemia.

WO 89/11521 describes in particular an industrial process for the extraction of mixtures having a high content in poly-unsaturated acids, also including EPA and DHA and their ethyl esters, from animal and/or vegetable oils. Mixtures of fatty acids, in particular EPA/DHA, obtained according to WO 89/11521, are indicated as particularly useful in the treatment of cardiovascular pathologies.

Therefore, object of the present invention is the use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute.

For convenience of description, eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester are mentioned here below respectively as "EPA" and "DHA".

An essential fatty acid, according to the invention, is preferably a fatty acid having a high content in EPA and DHA, for example with a content in EPA and DHA higher than 25% by weight, preferably from about 30% to about 100% by weight, in particular about 85%.

EPA is present in the EPA/DHA mixture preferably in a percentage ranging from 25% to about 45% by weight and DHA is present preferably in a percentage ranging from 55% to about 75% by weight.

At any rate, the most preferred ratio between EPA and DHA is about 0.6-1.1/1.3-1.8; in particular about 0.9/1.5.

An essential fatty acid according to the present invention can be obtained by known methods, e.g. as described in US Patent No. 5,656,667 and WO 89/11521.

Object of the present invention is also the use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, where the medicament is for combined therapy with another therapeutic agent.

The term "another therapeutic agent" means an additional single agent or two or more additional agents, preferably from 2 to 10, in particular from 2 to 6 according to physician's instructions, which may be administered in combination, namely either along or separately (substantially simultaneously or sequentially) with the essential fatty acid containing the mixture of EPA and DHA.

Examples of therapeutic agents for such a prophylaxis or combined therapy according to the invention are ACE-inhibitors, NEP-inhibitors, ACE/NEP-inhibitors, angiotensin II converting enzyme inhibitors, diuretics, positive inotropic drugs, phosphodiesterase inhibitors, arteriolar and venular vasodilators, beta-blockers and digitalis glycosides, or a mixture thereof.

NEP means degradation peptidase of atrial natriuretic peptide (ANP).

Examples of ACE-inhibitors are: captopril, enalapril, lisinopril, fosinopril, cilazapril, benazapril, perindopril, quinapril, ramipril, trandolapril and delapril, in particular cilazapril, captopril and enalapril.

Examples of ACE/NEP-inhibitors are: omapatrilat, sampatrilat and L-phenylalanine,N-[(2S)-2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-4-(2-thiazolyl) (compound Z13752A, a product of Zambon Company).

Examples of angiotensin II receptors antagonists (angiotensin II converting inhibitors) are: candesartan, valsartan and losartan.

Examples of diuretics are: hydrochlorothiazide, trichlormethiazide, chlorothiazide, chlortalidone, triamterene, clofenamide, furosemide, torasemide, ethacrynic acid, etozoline, spironolactone and amiloride, if the case in association with potassium sparing drugs, which are well known in the art, in particular furosemide and hydrochlorothiazide.

Examples of dopaminergic agents are dopamine and ibopamine.

Examples of phosphodiesterase inhibitors are: amrinone, milrinone, enoximone and bucladesine, in particular amrinone and enoximone.

Examples of arteriolar and venular vasodilators are: hydralazine and isosorbide dinitrate.

Examples of beta-blockers are: visoprolol, practotol, metoprolol, bucindol, carvedilol, atenolol, bisoprolol, celiprolol and nevibolol, in particular visoprolol, carvedilol and metoprolol.

Examples of digitalis glycoside agents are: acetyl digitoxin, acetyldigoxin, digitoxin, digoxin, lanatoside C, deslanoside, methyldigoxin and gitoformat, in particular digitoxin, digoxin, acetyldigoxin and metidigoxin.

Examples of positive inotropic agents are: pimobendan and vesnarinone, in particular pimobendan.

A further object of the invention is a method for preventing and treating a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an unsaturated essential acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

A further object of the invention is a method to prevent and treat a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), in combination with another therapeutic agent.

The term "in combination" means that the essential fatty acid containing the mixture EPA+DHA and the other therapeutic agent are administered in such an amount and separated by such administration times as to produce a therapeutic effect.

The use of an essential fatty acid according to the invention is extremely useful in the prevention and treatment of cardiac insufficiency and heart failure both chronic and acute, in particular, in the elderly people, e.g. older than 60 years, in subjects with other further cardiopathic forms and, in particular, in subjects surviving a myocardial infarction, thanks to the fact that this is a well tolerated drug.

The amount of essential fatty acid to be administered to a patient, either as a single therapeutic agent or in combination with another therapeutic agent, depends on its EPA/DHA content. In particular, the amount of essential fatty acid having a EPA/DHA content of about 85%, to be administered to a patient, may vary from about 0.7 g to about 1.5 g daily. More specifically, the amount of essential fatty acid, with a EPA/DHA content of about 85% and an EPA/DHA ratio of about 0.9/1.5 is of about 1 g daily.

This amount of product may be administered in the form of several daily divided doses or preferably as a single dose, in order to reach the desired blood level. Of course, the clinician may vary the amount of product (or mixture with another therapeutic agent) to be administered, basing on the patient's conditions, age and weight.

The amount of additional therapeutic agent, when administered in combination with the essential fatty acid, is substantially the amount usually employed by the clinician in therapy. At any rate, the clinician may vary the amount of this additional drug (or mixture of additional drugs) basing on the patient's clinical picture.

The combined use of an essential fatty acid according to the invention and of another therapeutic agent produces a synergic or superadditive effect, namely an improvement of the patient's clinical picture surely greater than the one observed with the administration of the essential fatty acid or of the "other therapeutic agent" alone. Moreover, the greater therapeutic effect in the combined treatment is not accompanied by an increased toxicity.

Therefore, the present invention provides the clinician with a new method of therapeutic treatment effective for preventing and treating cardiac insufficiency and heart failure or at least improving the conditions of a patient suffering from such heart diseases or improving his/her quality of life. Indeed, on the basis of clinical markers, which are to-day useful to understand the various stages of cardiac insufficiency and

progressive evolution towards an overt heart failure, the clinician can make use of the present invention and prevent or at least delay its evolution.

The pharmaceutical preparations according to the present invention can be prepared by methods well known in the art. A preferred route of administration is the oral one, but the physician may use to adopt other routes of administration e.g. the parenteral one.

The therapeutic agent for the combined therapy, according to the present invention, can be formulated as well known in the art.

The essential fatty acid can be formulated, for example, in the form of gelatin capsules as stated below.

Gelatin capsules

According to the methods known from pharmaceutical technique, capsules are prepared with the following composition and containing 1 g of active ingredient (85% EPA-DHA) in each capsule.

Formulation 1.

- EPA ethyl ester	525 mg/capsule;
- DHA ethyl ester	315 mg/capsule;
- d-alpha-tocopherol	4 IU/capsule;
- gelatin	246 mg/capsule;
- glycerol	118 mg/capsule;
- red iron oxide	2.27 mg/capsule;
- yellow iron oxide	1.27 mg/capsule.

Formulation 2.

- Ethyl esters of poly-unsaturated fatty acids	1000 mg;
- with content in ethyl esters of ω-3 poly-unsaturated acids (eicosapentaeonic EPA, docosahexaenoic DHA)	850 mg;
- d,l-alpha-tocopherol	0.3 mg;
- gelatin succinate	233 mg
- glycerol	67 mg;
- sodium p-hydroxybenzoate	1.09 mg;
- propyl sodium p-hydroxybenzoate	0.54 mg.

CLAIMS

1. Use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and of docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute.

2. Use according to claim 1, wherein the medicament is for the combined therapy with another therapeutic agent.

3. Use according to claims 1 or 2, wherein the content in EPA+DHA in the mixture is higher than 25% by weight.

4. Use according to claim 3, wherein the content in EPA+DHA is from about 30% and about 100% by weight.

5. Use according to claim 3, wherein the content in EPA+DHA is about 85% by weight.

6. Use according to claim 3, wherein in EPA+DHA mixture, EPA is present in an amount ranging from about 25% to about 45% by weight and DHA is present in an amount ranging from about 55% to about 75% by weight.

7. Use according to claim 3, wherein the EPA/DHA ratio is about 0.6-1.1/1.3-1.8.

8. Use according to claim 5, wherein the EPA/DHA ratio is about 0.9/1.5.

9. Use according to claim 5, wherein the essential fatty acid is administered by oral route at a dose ranging from about 0.7 g and about 1.5 g daily.

10. Use according to claim 1 or 2, wherein the heart disease is cardiac insufficiency.

11. Use according to claim 1 or 2, wherein the heart disease is heart failure.

12. Use according to claim 11, wherein heart failure is chronic or acute.

13. Use according to claim 2, wherein the therapeutic agent for the combined therapy is chosen from ACE-inhibitors, NEP-inhibitors, ACE/NEP-inhibitors, angiotensin II converting enzyme inhibitors, diuretics, positive inotropic drugs, phosphodieserase inhibitors, arteriolar and venular vasodilators, beta-blockers and digitalis glycosides or a mixture thereof.

14. Use according to claim 13, wherein the therapeutic agent for the combined therapy is chosen from one or more agents chosen from cilazapril, captopril, enalapril, candesartan, valsartan, losartan, furosemide, hydrochlorothiazide, dopamine, ibopamine, amrinone, enoximone, hydralazine, isosorbide dinitrate, visopropol, carvedilol, metoprolol, digitoxin, digoxin, acetyldigoxin, metidigoxin, pimobendan, omapatrilat, sampatrilat and compound Z13752A.

15. Use according to each of the previous claims, wherein the treated patient is a person older than 60 years.

16. Use according to each of the previous claims wherein the treated patient is a person suffering from other cardiopathic disorders.

17. Use according to each of the previous claims, wherein the treated patient is a person who survived a myocardial infarction.

18. A method for preventing and treating a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an unsaturated essential acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

19. A method to prevent and treat a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), in combination with another therapeutic agent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/00507

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P9/00 A61K45/06 A61K31/23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARCHIOLI, R. ET AL: "The results of the GISSI-Prevenzione trial in the general framework of secondary prevention" EUROPEAN HEART JOURNAL (2000), 21(12), 949-952 , XP008002773 page 949 page 951, left-hand column	1-4, 6-13, 15-19
X	EP 0 699 437 A (PROSPA BV) 6 March 1996 (1996-03-06) page 3, line 9-11; claims; example 4 page 3, line 19	1-8,11, 16,18,19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2002	13/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89 11521 A (STAROIL LTD) 30 November 1989 (1989-11-30) cited in the application page 8, line 17 -page 9, line 4 page 10, line 24 -page 11, line 6 page 18, line 13-19 page 38, line 5,6; claims 12,16	1,3-12, 16-19
A	PAKALA, R. ET AL: "Vascular smooth muscle cells preloaded with eicosapentaenoic acid and docosahexaenoic acid fail to respond to serotonin stimulation" ATHEROSCLEROSIS (SHANNON, IRELAND) (2000), 153(1), 47-57 , XP001075031 page 55, right-hand column, paragraphs 3,4	1,10-12, 16-19
A	AVIJIT HAZRA ET AL: "Pharmacology and Therapeutic Potential of the n-3 Polyunsaturated Fatty Acids, Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in Fish Oils" INDIAN JOURNAL OF PHARMACOLOGY, vol. 31, August 1999 (1999-08), pages 247-264, XP008002754 page 248, right-hand column, paragraph 3 page 250 page 252; table 1 page 256	1-4, 7-13, 16-19
A	WO 98 10085 A (COLLATERAL THERAPEUTICS) 12 March 1998 (1998-03-12) page 2, line 4-7	1,10-12, 16-19
A	DATABASE WPI Week 199528 Derwent Publications Ltd., London, GB; AN 1995-209437 XP002197622 & JP 07 118229 A (FUJISAWA PHARM CO LTD), 9 May 1995 (1995-05-09) abstract	1,11,12, 16,18,19
A	US 5 683 997 A (BUEHLMAYER PETER ET AL) 4 November 1997 (1997-11-04) column 4, line 11,12 column 4, line 14-18	1,10-12, 16-19
A	EP 0 689 838 A (UNITIKA LTD) 3 January 1996 (1996-01-03) page 2, line 12-15	1,11,12, 16-19
A	US 2001/031857 A1 (MARKUS ASTRID ET AL) 18 October 2001 (2001-10-18) paragraph '0002!	1,10-12, 16-19

-/--

INTERNATIONAL SEARCH REPORT

	ional Application No
	PCT/EP 02/00507

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 587 269 A (TELECTRONICS NV) 16 March 1994 (1994-03-16) column 1, line 15-19	1,10-12, 16-19

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/00507

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0699437	A	06-03-1996	IT	1274734 B	24-07-1997
			DE	69506642 D1	28-01-1999
			DE	69506642 T2	22-07-1999
			DE	699437 T1	07-11-1996
			EP	0699437 A1	06-03-1996
			JP	8175988 A	09-07-1996
			US	5776978 A	07-07-1998
WO 8911521	A	30-11-1989	GB	2218984 A	29-11-1989
			AT	75502 T	15-05-1992
			CA	1334207 A1	31-01-1995
			CN	1040050 A ,B	28-02-1990
			DE	68901382 D1	04-06-1992
			WO	8911521 A1	30-11-1989
			EP	0409903 A1	30-01-1991
			ES	2017268 A6	16-01-1991
			GR	89100345 A	10-10-1991
			PT	90668 A ,B	30-11-1989
WO 9810085	A	12-03-1998	AU	741931 B2	13-12-2001
			AU	4251997 A	26-03-1998
			CN	1234835 A	10-11-1999
			EP	0934422 A2	11-08-1999
			US	6306830 B1	23-10-2001
			WO	9810085 A2	12-03-1998
			ZA	9708019 A	11-11-1998
JP 7118229	A	09-05-1995	NONE		
US 5683997	A	04-11-1997	AU	685767 B2	29-01-1998
			AU	5696694 A	04-07-1994
			CA	2151380 A1	23-06-1994
			WO	9413642 A1	23-06-1994
			EP	0673369 A1	27-09-1995
			FI	952804 A	07-06-1995
			HU	71557 A2	28-12-1995
			JP	8506097 T	02-07-1996
			NO	952289 A	09-06-1995
			NZ	258888 A	24-02-1997
EP 0689838	A	03-01-1996	JP	8012581 A	16-01-1996
			DE	689838 T1	10-10-1996
			EP	0689838 A1	03-01-1996
			KR	149114 B1	15-10-1998
			US	5571524 A	05-11-1996
US 2001031857	A1	18-10-2001	EP	1130027 A1	05-09-2001
			AU	5031801 A	12-09-2001
			WO	0164715 A2	07-09-2001
EP 0587269	A	16-03-1994	US	5324323 A	28-06-1994
			DE	69322562 D1	28-01-1999
			DE	69322562 T2	15-07-1999
			EP	0587269 A2	16-03-1994
			JP	6165827 A	14-06-1994